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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/748,003	12/30/2003	Nejat K. Egilmez	40543.0001	6565

26712 7590 12/30/2005

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EXAMINER	
FETTEROLF, BRANDON J	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 12/30/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/748,003	EGILMEZ, NEJAT K.	
	Examiner	Art Unit	
	Brandon J. Fetterolf, PhD	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 October 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) *12-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Egilmez, Nejat

DETAILED ACTION

The Election filed on October 17, 2005 in response to the Restriction Requirement of 09/29/2005 has been entered. Applicant's election of Group I, claims 1-11, as specifically drawn to a method of inhibiting the growth of gastrointestinal tumors comprising the steps of orally administering to an individual with one or more gastrointestinal tumors, a formulation comprising polymeric microspheres encapsulating a drug composition has been acknowledged.

In this instance, Applicants argue that simply because the intended recipients are different, it cannot be held that the materials used are divergent because the active steps are the same. As such, Applicants request rejoinder of Groups I and II.

This argument has been considered but is not found persuasive.

With regards to Applicants argument that it cannot be held that the materials used are divergent because the active steps are the same, the Examiner recognizes that inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case, the two methods, treating and/or preventing the growth of gastrointestinal tumors, do not appear to be capable of use together because two distinct populations, i.e. one with a tumor and one who does not have a tumor, may be used in each of the methods. Furthermore, it would appear a compound used to treat a cancer would have a different mode of operation, function and different effect than a compound used for the prevention.

For these reasons, the Restriction Requirement is deemed proper and therefore, made Final.

Claims 1-26 are currently pending.

Claims 12-26 are withdrawn from consideration as being drawn to a non-elected invention.

Claims 1-11 are currently under consideration.

Information Disclosure Statement

The Information Disclosure Statement filed on 10/17/2005 is acknowledged. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information

disclosure statement is being considered by the examiner. A signed copy of the IDS is attached hereto.

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-5 and 7-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mathiowitz et al. (US 2001/0043914, 2001) in view of Mathiowitz et al. (6,235,313, 2001).

Mathowitz et al. ('914) teach a method of treating a tumor comprising administering to an individual a formulation comprising a polymeric microsphere containing IL-12, wherein the administration of the formulation is effective to treat said tumor (abstract). With regards to the polymeric microsphere, the '914 publication teaches that polymeric microsphere refers to polymeric particles including, but not limited to, polyanhydrides such as poly(lactide-co-glycolide), polycaprolactone, poly(fumaric-co-sebacic)acid and polyacrlylic acid (page 5, paragraph 0047 to 0049 and page 12, paragraph 0105). With regards to the tumor, Mathowitz et al. teach that the tumors include, but are not limited to, colon and rectum cancer, and esophageal cancer (page 4, paragraph 0043). The '914 publication further teaches that the concentration of the IL-12 microspheres may be at a dose of about 0.2-70 micrograms for an adult of 70Kg body weight or at a dose of 3.5-21 micrograms (page 11, paragraph 0092). Moreover, Mathowitz et al teach that the polymeric microspheres can be prepared by a phase inversion nanoencapsulation method (page 6, paragraph 0057).

Mathowitz et al. do not explicitly teach that the formulation comprising a polymeric microsphere containg IL-12 is administered orally. Nor does Mathowitz et al. explicitly teach that the polymeric microspheres are prepared by hot melt method.

Mathowitz et al. ('210) teach bioadhesive microspheres for use in drug delivery systems, wherein the microspheres can be composed of bioerodible polymers such as polyanhydrides, poly[lactide-co-glycolide] and polyothoesters (column 7, lines 22-23). With regards to the microspheres, the patent teaches that the microspheres can be fabricated from different polymers using a variety of different methods including, but not limited to, hot melt microencapsulation (column 11, line 55 to column 12, line 55). Mathowitz et al. further disclose that the agents may be administered orally, wherein oral administration is advantageous with respect to both cost considerations as well as patient compliance and comfort (column 3, lines 50-57).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to administer the polymeric microsphere comprising IL-12 as taught by Mathowitz et al. ('914) orally in view of the teachings of Mathowitz et al. ('210). One would have been motivated to do so because as taught by Mathowitz et al. ('210), oral administration of agents offers advantages over systemic injection with respect to cost considerations as well as patient compliance and comfort. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by administering to a patient a polymeric microsphere comprising IL-2 orally in view of the teachings of Mathowitz et al. ('210), one would achieve a cost effective and patient compliant method of treating cancer.

Claims 1-3, 5-6 and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Giardiello et al. (Gut, 1996; 38; 578-581) in view of Mathowitz et al. (US 6,235,313, 2001).

Giardiello et al. teach a method of inhibiting the growth of colorectal adenomas comprising the steps of orally administering sulindac to an individual with a gastrointestinal tumor in an amount effective to inhibit the growth of the tumor (Abstract). With regards to the effective amount, the reference teaches that 150 mg of sulindac was given per dose (Abstract, *Results*).

Giardiello et al. does not explicitly teach that sulindac is encapsulated in a polymeric microsphere or any of the properties recited therein.

Mathowitz et al. teach bioadhesive polymers in the form of microcapluses containing drugs or other bioactive substances, which serve as therapeutics for the treatment of diseases of the

gastrointestinal tract (abstract). With regards to the microcapsules, e.g. microspheres, the patent teaches that the microcapsules may be composed of bioerodible polymers such as polyanhydrides, poly[lactide-co-glycolide] and polyothoesters (column 7, lines 22-23), wherein the microcapsules can be fabricated from different polymers using a variety of different methods including, but not limited to, hot melt microencapsulation (column 11, line 55 to column 12, line 55). Mathowitz et al. further teach that the bioadhesive molecules provide a drug delivery formulation that is useful for drug delivery via the mucosal membranes providing greater drug bioavailability (column 2, paragraph 0015 and page 1, paragraph 0005).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to encapsulate sulindac with a microcapsule in view of Mathowitz et al. One would have been motivated to do so because as taught by Mathowitz et al., mucoadhesion results in a substantially improved bioavailability. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by encapsulating sulindac with a microcapsule as taught by Mathowitz et al, one would achieve an a method of increasing the bioavailability of sulindac for cancer treatment.

Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over Giardiello et al. ((Gut, 1996; 38; 578-581) in combination with Mathowitz et al. (US 6,235,313, 2001) in further view of Egilmez et al. (Cancer Research 2000; 60: 3832-3837, IDS).

The combination of Giardiello et al. and Mathowitz et al. teach, as applied to claims 1-3, 5-6 and 8 above, a method of inhibiting the growth of colorectal adenomas comprising the steps of orally administering sulindac to an individual with a gastrointestinal tumor in an amount effective to inhibit the growth of the tumor, wherein the sulindac is encapsulated in a polymeric microsphere. With regards to the microsphere, the combination teaches that the microspheres can be fabricated using solvent evaporation, a hot melt microencapsulation, and spray drying (column 11, line 65 to column 12, line 4 of 6,235,313).

The combination of Giardiello et al. and Mathowitz et al. do not explicitly teach that the polymeric microsphere was fabricated by a phase inversion method.

Egilmz et al. describe a novel technology referred to as PIN, i.e., phase inversion nanoencapsulation (Mathiowitz et al. Nature 1997; 386: 410-414, specifically page 411, 1st column, 1st

paragraph) that encapsulates biologically active molecules into polymer microspheres with high efficacy (page 3832, 2nd column, 2nd paragraph). Specifically, the reference teaches that the PIN technology offers advantages over the prior methods such as not requiring vigorous stirring/sonification during the formation of emulsions, and labile proteins are efficiently encapsulated without denaturation or losses to aqueous non-solvent baths (page 3832, 2nd column, 2nd paragraph).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was to encapsulate sulindac into a polymer microsphere as taught by Mathowitz et al. in view of the teachings of Egilmez et al.. One would have been motivated to do so because as taught by Egilmez et al., PIN technology offers advantages over the prior methods such as not requiring vigorous stirring/sonification during the formation of emulsions, and labile proteins are efficiently encapsulated without denaturation or losses to aqueous non-solvent baths (page 3832, 2nd column, 2nd paragraph). Thus, one of ordinary skill in the art would have a reasonable expectation of success that by encapsulate sulindac into a polymer microsphere as taught by Mathowitz et al. in view of the teachings of Egilmez et al., one would achieve an a method of encapsulating sulindac into a polymer microsphere with high efficacy.

Therefore, NO claim is allowed.

JEFFREY SIEW
SUPERVISORY PATENT EXAMINER
12/22/05

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J. Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached on Monday through Friday from 8:30 to 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeff Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Brandon J Fetterolf, PhD
Examiner
Art Unit 1642

BF